Amendments to the Drawings:

Applicants submit herewith replacement drawing sheets which include more clear copies of Figs. 1, 2, 4 and 7 as required by the Examiner.

Attachment: Replacement Sheets

REMARKS

By this Amendment, claims 1, 5, 17, 18, and 25 have been amended and claims 37-78 have been added. Claims 29-30 have been cancelled without prejudice and claims 31-36 stand withdrawn. Claims 1-28 and 37-78 are thus currently under examination in the present application. For the reasons set forth below, Applicants submit that the present amendments and arguments place this application in condition for immediate allowance.

As an initial matter, by virtue of the present amendments, new claims 37-78 have been added. These claims have been added to incorporate limitations previously presented in claim 1 and the claims that depended therefrom. Accordingly, no new matter has been added by these amendments.

In the Office Action, the Examiner referred to the fact that Applicants' Declaration inadvertently included the notation of "YES" under the category "Priority Not Claimed" despite the fact that it has been clear from the filing of the International application and the submission of the Certified Copy of the priority document that Applicants clearly made the priority claim and never intended not to. Indeed, the Declaration include the reference to the priority document under the box that states "I hereby claim FOREIGN PRIORITY", and there would have been no need to put anything in this box if Applicants had not intended to maintain their priority claim. In any event, Applicants submit herewith an Application Data Sheet which does not refer to "Priority not claimed" and submit that this further confirms the claim of priority in this application.

In the Office Action of August 20, 2008, the Examiner objected to claims 9, 10, 14, and 16 for reciting SEQ ID NOS that were not elected. Applicants acknowledge that the examination conducted in conjunction with the present Office Action was performed with regard to the elected species, namely the elected sequences of SEQ ID NOS: 1, 13, 15, and 17. However, Applicants have maintained the non-elected subject matter in the claims in order to reserve the right to request rejoinder of the non-elected species upon the allowance of the elected species. Upon later determination that these non-elected species are not able to be rejoined, Applicants will then cancel the non-elected species and reserve the right to file a continuation.

In the Office Action, the Examiner objected to the drawing figures 1, 2, 4 and 7 as having shaded areas which obscured text or plotted lines on a graph. Without addressing the merits of these objections, Applicants submit herewith clearer drawing figures which overcome any objection.

In the Office Action, the Examiner then rejected claims 1-30 under 35 U.S.C. §112, second paragraph as being indefinite. In particular, the Examiner made several minor objections to the wording of claims 1 and 17, and further asserted that claims 1, 18, and 25 were indefinite for including a broad range or limitation together with a narrow range or limitation that fell within the broader range. These rejections have now been rendered moot by virtue of the present amendments, which are discussed in more detail below. Accordingly, Applicants respectfully traverse the Examiner's rejections, insofar as applied to the claims as amended, and request that they be withdrawn.

With regard to the rejection of claims 1 and 17, the Examiner asserted that the term "e.g." rendered claim 1 indefinite as it was unclear whether the limitations following the phrase were part of the claimed invention and asserted that claim 17 was indefinite because the second sentence was unclear. By the present amendments, Applicants have removed the phrase "e.g. HBV present in a biological sample, possibly in the presence of a pharmaceutical product, preferably an antiviral agent" from claim 1 and have deleted the second sentence from claim 17.

With regard to the rejections of claims 1, 18, and 25 under 35 U.S.C. §112, second paragraph, these rejections have also been rendered moot by virtue of the present amendments. In particular, claim 1 has been amended to only refer to a pharmaceutical product; claim 18 has been amended to provide a specific range of amplification cycles; and, claim 25 has been amended to only refer to eukaryotic cells. Similarly, by the present amendments, claim 5 has also been amended to remove the phrase "and preferably comprising a restriction site in the overlapping part."

In the Office Action of August 20, 2008 the Examiner then made several rejections to the claims of the present application under 35 U.S.C. 103(a) as being unpatentable over Junker, et al. (Nucleic Acids Research. 15(24): 10117-10132 (1987)) and the dissertation of Garces, in combination with a variety of second references including: Weimer, et al. (Journal of Virology. 61(10): 3109-3113, Oct. 1987); GenBank No. AB048704; Norder, et al. (Virology. 198: 489-503 (1994); Schories, et al. (Journal of Hepatology. 33: 799-811 (2000)); Hasegawa, et al. (Journal of Virology. 68(3): 1651-1659, Mar. 1994); Jones (U.S. 2002/0072055); Halle (U.S. 6,303,308); McLauglin, et al.

(US 2003/0104395); Pachuk, et al. (Gene. 243: 19-25 (2000)); Wilson (U.S. 6,001,557); Sells, et al. (Proc. Nat. Acad. Sci. USA 84: 1005-1009, Feb. 1987); and, Delany, et al. (Antimicrobial Agents and Chemotherapy. 43(8): 2017-2026, Aug. 1999). In particular, although the Examiner acknowledges in the Office Action that Junker does not teach polymerase chain reaction (PCR) amplification of HBV nucleic acids using at least two primer pairs selected to obtain at least two different fragments and that Garces does not teach PCR amplification of HBV genomic fragments to obtain greater-than-genome length constructs, it would have been obvious to one of ordinary skill in the art to obtain further fragments by PCR. For the reasons set forth below, Applicants respectfully traverse these rejections and request that they be withdrawn.

The claims of the present application are directed toward methods for measuring the replication capacity of HBV and, in particular, HBV present in a biological sample. The claimed methods provide for PCR amplification from a specific strain of HBV that is present in a biological sample, before the cloning of fragments or the production of a corresponding pregenomic RNA (pgRNA). In this regard, it is thus noted that by use of the presently-claimed methods, it is not necessary to know beforehand which particular strain of HBV may be present in a sample, as the presently-claimed methods are capable of recovering and amplifying any HBV strain. The primer pairs described and claimed in the present application are designed such that it is possible to recover nucleic acids from any or a vast number of HBV strains and clone a replication-competent HBV DNA genome that corresponds to the genome of the particular strain of HBV in a sample, including previously unknown strains of HBV.

In this regard, Applicants have unexpectedly discovered that primer pairs can be designed which are sufficiently universal such that by using the primers pairs all of the necessary nucleic acids can be recovered from an HBV strain and the resulting HBV fragments can then be reassembled to provide a linear continuous DNA sequence capable of being transcribed into pgRNA in susceptible cells. From this pgRNA, HBV replication and the production of the particular HBV strain present in a biological sample can be analyzed to determine not only the replication capability of the particular HBV strain, but also its sensitivity to a variety of pharmaceutical products, such as antiviral agents. Accordingly, the methods described and claimed in the present application allow for the recovery of known or unknown strains of HBV by PCR amplification and the reconstruction thereof such that the susceptibility of an HBV strain to particular pharmaceutical products may be tested and the most appropriate treatment selected.

Neither Junker or Garces, either alone or in combination, teach or suggest the recovery of HBV nucleic acids from a biological sample, much less teach or suggest the recovery of these nucleic acids such that a linear continuous DNA sequence can be obtained and transcribed into a pgRNA that corresponds to the particular HBV strain that is present in a sample. Instead, Junker relates to the expression and replication of an HBV genome that is under the control of a foreign promoter. Indeed, as the Examiner acknowledges in the Office Action, Junker does not teach or suggest PCR amplification of HBV nucleic acids using at least two primer pairs to obtain at least two different fragments. Junker merely discloses the cloning of an HBV genome into a plasmid

wherein the viral pgRNA is put under the transcriptional control of a human metallothionein II_A promoter.

Garces, on the other hand, relates to a method for constructing a greater-than-genome length HBV vector under the control of a heterologous promoter. However, as the Examiner also acknowledges in the Office Action, Garces does not teach or suggest amplifying all HBV genomic fragments to obtain a greater-than-genome length construct. Instead, Garces uses PCR amplification to produce a short HBV genomic fragment and then makes a final construct by ligation of the short HBV genomic fragment to a known linear, full-length HBV genome. Accordingly, neither Junker or Garces, alone or in combination, teach or suggest a method whereby PCR is used to amplify nucleic acids from a strain of HBV present in a biological sample to obtain at least two different amplified genomic fragments, which can then be used to produce the corresponding pgRNA.

In further contrast to the cited prior art references, Applicants additionally submit that there are surprising and unexpected results associated with the claimed invention that are not found in the cited references or in the art in general. Prior to the claimed invention, it was not thought that a method could be developed that allowed for the analysis of HBV replication and the testing of pharmaceutical products on field strains of HBV, particularly unidentified strains present in biological sample. Surprisingly, however, the claimed method which makes use of universal primer pairs to obtain at least two different amplified HBV genomic fragments was found to amplify all of the

necessary fragments from an HBV genome such that the fragments could be recovered and assembled to produce a corresponding pgRNA in a transfected cell.

Junker and Garces do not teach or suggest this unexpected method of the present invention. These references do not teach or suggest capturing nucleic acids in a sample using universal primer pairs to obtain a continuous DNA sequence that is capable of being transcribed into a pgRNA. Moreover, neither Junker or Garces, alone or in combination, even remotely suggest that it is possible to capture a nucleic acid of an unknown strain of HBV in a biological sample, amplify and transcribe the nucleic acid, and then test the HBV strain with a series of available pharmaceutical products. Only using impermissive hindsight, using the present disclosure as a blueprint, would one of ordinary skill in the art know how to design a pair of universal primers to capture an unknown HBV strain in a biological sample and practice the invention, as claimed.

The secondary references cited by the Examiner add nothing further in this regard. The teachings of the secondary references fail to in any way teach or suggest the amplification of nucleic acids from known or not-yet identified HBV strains from a biological sample, and do not teach or suggest the use of two primer pairs that are selected so as to obtain at least two different HBV fragments that can then be used to assemble a linear continuous DNA sequence capable of being transcribed into pgRNA.

Accordingly, Applicants respectfully submit that the present invention is not rendered obvious by the cited references and that the claims of the present application are clearly patentable over those references. Applicants thus submit that the Examiner's

rejections on the basis of those references is respectfully traversed and should be withdrawn.

In light of the amendments and arguments provided herewith, Applicants submit that the present application overcomes all prior rejections and objections, and has been placed in condition for allowance. Such action is respectfully requested.

Respectfully submitted,

Date: December 22, 2008

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